

### REMARKS

The April 9, 2003 Official Action has been carefully considered. In view of the present amendments, the declarations submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the April 9, 2003 Official Action. The initial due date for response, therefore, was July 9, 2003. A petition for a three (3) month extension of the response period is presented with this submission, which is being filed within the three (3) month extension period.

In the April 9, 2003 Official Action, the 35 U.S.C. §102(b) rejection, in which Peterson et al., Reeck et al. and Kothari et al. are each cited as alleged anticipations of claims 25, 27, 34, 42, 44, 48 and 66, has been repeated and made final. Claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable in view of the above-mentioned Peterson et al., Reeck et al. and Kothari et al. references, taken together with Burton et al. (U.S. Patent No. 5,652,348) and the Sigma catalog. According to the Examiner, one of ordinary skill in the art would have been motivated from the disclosures of the cited references to modify the solid phase product of Peterson et al., Reeck et al., Kothari et al. and Burton et al. by substituting Bis-Tris biological buffer for the Tris component of ECTHAM cellulose, as allegedly suggested by the Sigma catalog, for the expected benefit of extending the pH range of ionization in a method of immobilizing nucleic acids.

Claims 25-31, 34 and 42-68 also stand finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable in view of Peterson et al., Reeck et al., Kothari et al. and the Sigma catalog as applied in the above-noted §103 rejection, and further in view of Arnold, Jr. et al. (U.S. Patent No. 5,599,667), Hornes et al. (U.S. Patent No. 5,512,439) and Sommerton et al. (U.S. Patent No. 6,060,246). It is the Examiner's position that one of ordinary skill in the art would have been motivated to modify the solid phase product of Peterson et al., Reeck et al. and Kothari et al., as suggested by the purported disclosure of the Sigma catalog, for the isolation of nucleic acids, in accordance with the disclosures of Arnold, Jr. et al., Hornes et al. and Sommerton et al. The Examiner asserts in this regard that Arnold et al. suggests that the expected benefit of using magnetic beads in order to improve the handling and speed of assays for isolation and analysis of nucleic acids, that Sommerton et al. suggests the expected benefit of using ionizable amine groups bound to a solid phase support for the rapid isolation and detection of nucleic acids in a polynucleotide-containing sample, and that Hornes et al. suggests the expected benefit of using paramagnetic beads to improve handling of the beads and quantitative isolation and analysis of nucleic acids.

Claims 25-34 and 42-68 are also finally rejected under 35 U.S.C. §103(a) as allegedly unpatentable in view of the combined disclosures of Peterson et al., Reeck et al., Kothari et al., the Sigma catalog, Arnold, Jr. et al., Hornes et al. and Sommerton et al., as noted above, and further in view of Tooley

et al. (U.S. Patent No. 5,874,221) and Cobbs et al. (U.S. Patent No. 5,916,746). The Examiner contends in this regard that one of ordinary skill in the art would have been motivated to modify the ionizable groups attached to a solid support used in a method of isolation of nucleic acids as disclosed in Peterson et al., Reeck et al. and Kothari et al. as modified by the disclosure of the Sigma catalog, and in accordance with the alleged suggestions of Arnold, Jr. et al., Hornes et al. and Sommerton et al., as discussed above, by utilizing a nucleic acid binding pipet tip as disclosed in Tooley et al. or a multi-well plate as disclosed in Cobbs et al. for the expected benefit of improving the speed, reducing the number of steps in the method, thereby simplifying the method, improving yield and eliminating sources of handling errors.

The April 9, 2003 Official Action also sets forth certain new grounds of objection and rejection. Specifically, claims 1-34 and 38-64 are considered objectionable based on the British form of spelling the term "ionisable" and appropriate correction is required. In addition, claims 25-34 and 42-63 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out the subject matter that applicant regards as the invention. In this connection, the Examiner asserts that there is insufficient antecedent basis for the recitation "the solid phase" and "the solid support" in claims 25, 42, 51 and 59. The Examiner also contends, with respect to recitations (i), (ii) and (iii) in claim 34, which pertain to the "plurality of ionizable groups",

that it is not clear if all, one or various combinations of these recitations are required in the water-soluble product of claim 34. The Examiner also points out that there is insufficient antecedent basis for the recitation of "the polymer" in claim 63, line 1.

The Examiner further contends that claims 25, 27, 28, 34, 42, 44 and 48 are anticipated by the disclosure of Burton et al., which was also relied on in support of the obviousness rejection of claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66, as noted above.

The foregoing objections and rejections constitute all of the grounds set forth in the April 9, 2003 Official Action for refusing the present application.

In accordance with the present amendment, a pKa range is recited in independent claims 25, 34, 42, 51 and 59. There is support for a pKa range of "about 4.5 to about 8.5", where the ionizable group is positively charged in the present specification at page 5, lines 9-13.

Consequential amendments have been made in claims 26, 34 and 42 to remove the biological buffers from the list recited in those claims, which have initial pKa's which fall outside of the pKa range of about 4.5 to about 8.5.

New claims 69-73 are presented herewith. These claims specify that the pKa of the plurality of ionizable group is between 5.0 and 6.5. Support for these claims is found in the present specification at page 5, lines 11-14.

Also in accordance with this amendment, the spelling

of "ionizable" has been made uniform throughout the claims; the term "solid support" has been eliminated from claims 25, 42, 51 and 59, which claims have been amended to provide proper antecedent basis for the recitation "solid phase"; claim 34 has been amended to make clear that items (i), (ii) and (iii) may be taken in the alternative, i.e. either (i) or (ii) or (iii), the latter including both (i) and (ii); and the dependency of claim 63 has been amended to provide proper antecedent basis for the recitation of "the polymer" in line 1 thereof.

No new matter has been introduced into this application by reason of the amendment presented herewith, entry of which is hereby requested.

As a result of the foregoing amendment, the new objections to the claims and new grounds of rejection under 35 U.S.C. §112, second paragraph have been overcome. Thus, the only matters remaining to be addressed are the various prior art rejections set forth in the April 9, 2003 Official Action. Those grounds of rejection cannot be maintained in view of the present amendment and are, therefore, respectfully traversed.

Before addressing the various prior art rejections, applicant wishes to clarify an apparent misinterpretation by the Examiner of the subject matter encompassed by claim 34. Claim 37 is directed to a water-soluble product for extracting nucleic acid from a sample. Thus, the product, *per se*, is water-soluble. By contrast, claims 25, 42, 51 and 59 are all directed to a product comprising a solid phase which reversibly binds nucleic acid present in a sample. These claims specifically require a

plurality of positively ionizable groups immobilized on a solid phase. Claim 34 has no corresponding recitation. Thus, the Examiner is in error in stating, at page 8 of the April 9, 2003 Official Action, that claim 34 is directed "to a solid phase product which is water soluble...."

A. The §102 Rejections Based on Peterson et al, Reeck et al., Kothari et al. and Burton et al. Cannot be Maintained in View of the Amendment and Declaration Evidence Presented Herewith

Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the reference cited as evidence of lack of novelty. In re Arkley, 172 U.S.P.Q. 524 (C.C.P.A. 1972). Applying this rule of law to the present case, the 35 U.S.C. §102 rejections of claims 25-27, 34, 42-44, 48, 51, 52 and 66 based on Peterson et al., Reek et al., Kothari et al. or Burton et al., considered singly or together, are improper because the subject matter of those claims is nowhere identically disclosed or described in the cited references.

As currently amended, all of the independent claims call for a pKa range of "about 4.5 to about 8.5". This recitation serves to establish the patentability of all of the pending claims in relation to the prior art of record herein. This fact is clearly demonstrated by the Declaration of Matthew Baker and the Declaration of Garry Harper, which are submitted herewith. The Declaration of Matthew Baker avers that ECTHAM cellulose was prepared according to the procedure of Peterson et al. *supra*, and a sample was provided to Garry Harper for

measurement of the pKa. The Declaration of Garry Harper sets forth the methodology used for determining the pKa of ECTHAM cellulose, which was also used to measure the pKa of DEAE Sepharose, DEAE Sephadex A50 and a sample of Bis-Tris magnetic beads, respectively. The pKa measurement of the two commercial ion exchangers and a representative example of the charge switch material of the present invention was performed as a basis of comparison with that of ECTHAM cellulose. The pKa values measured by Dr. Harper were as follows: ECTHAM cellulose = 12.55; DEAE Sepharose = 14.16; DEAE Sephadex A50 = 14.23; and Bis-Tris charge switch beads = 5.49. Thus, there is a clear difference between the pKa of the claimed charge switch material and ECTHAM cellulose.

Based on the above-noted pKa measurements, the Declaration of Matthew Baker concludes that the pKa of ECTHAM cellulose (pKa =12.55) "is too high to make it useful as a charge switch material", in accordance with the present invention. See paragraph 8 of the Declaration of Matthew Baker. The pKa measurements reported in the declarations submitted herewith plainly show that mild pH or salt conditions are unlikely to result in charge switch type purification of nucleic acid if ECTHAM cellulose were used in the manner suggested by the Examiner to purify nucleic acid.

The Examiner's reliance on Burton et al. in rejecting claims 25, 27, 28, 34, 42, 44 and 48 under 35 U.S.C. §102(e) is also misplaced. Burton et al. discloses a class of chromatography resins that are used in hydrophobic interaction

chromatography for purifying proteins, and in particular enzymes such as chymosin and subtilisin from cultures. The resins have ligands appended to them which possess ionizable ligands, including some amines. However, the resins disclosed in Burton et al. are used quite differently in comparison to the charge switch materials of the present invention. In particular, the materials of Burton et al. employ the hydrophobic properties of the proteins and the resins to cause proteins present in aqueous mixtures to bind to the resins at high pH and under high salt conditions. The binding also requires that the target protein has a hydrophobicity different from that of the contaminants. See column 9, line 64 to column 10, line 16 of Burton et al. Even under these conditions, Burton et al. notes at column 9, lines 57-62 that the disclosed resins are not specific for the target protein and that "a significant level of non-target protein binding may occur". The proteins are then desorbed from the resins by reducing pH or desalting.

Although Burton et al. refers generally to "target compounds", it is primarily concerned with the purification of proteins, and in particular enzymes. The specific examples provided in the application all concern the purification of the proteins chymosin and subtilisin. Indeed, an essential purpose of the resins disclosed in Burton et al. is to avoid binding nucleic acid which is (presumably) present as a contaminant in the cultures from which the target proteins are purified. Moreover, the reliance in Burton et al. on using salting to achieve binding would clearly make the materials of Burton et al.



unsuitable for the purification of nucleic acid, given the teaching of Burton et al., as the large quantities of salt present in a "purified" sample would make it unusable in many analytical methods that employ nucleic acid, most notably in PCR.

In the Office Action, the Examiner particularly refers to column 8, lines 18-33 and column 12, lines 26-52 of Burton et al., arguing that this passage discloses water soluble solid phases comprising a plurality of ionizable groups consisting of polyamine or histidine. A careful reading reveals, however, that the resins disclosed in Burton et al. are not water soluble, in view of the description of solid support matrix or solid matrix provided in the section bridging columns 7 and 8. On the contrary, as the materials of Burton et al. rely on hydrophobic interaction to achieve binding they must be insoluble. This is confirmed by the description and examples which show that the materials of Burton et al. are not soluble in use, e.g. see examples VIII ("Resins ..were packed in disposable columns...") and example IX ("One sample of the resin...was suspended in load buffer and left to settle..."). Thus, claim 34 is certainly novel when considered in relation to Burton et al. in view of this difference.

Moreover, in regards to nature of the ligands disclosed in Burton et al., claims 25 and 42 of this application call for (1) biological buffers including amine groups, (2) polyhydroxylated amines, and (3) histidine and polyhistidine, all of these groups having a pKa between about 4.5 and about 8.5. For all of these groups, there is no disclosure in Burton et al.

of the pKa range reacted in claims 25 and 42. The only reference to pKa in Burton is at column 12, line 65 onwards, referring to ligands based on phenol or substituted phenol.

Furthermore, considering the biological buffers and polyhydroxylated amines first, these specific materials are novel in relation to the general disclosure in Burton et al. at column 8, lines 23-27 that the ligands may generically include amine groups. They are novel in relation to the specific disclosure provided in Burton at column 12 as the listed amines are not polyhydroxylated and none of the biological buffers claimed by applicant overlap with Burton et al.

As regards, histidine and polyhistidine, the disclosure at column 8, is again generic stating that the ionizable groups can be histidyl groups. The specific materials listed in column 12, however, mention histamine, which is different from histidine, or the use of halotrosines such as "fluoro, chloro, bromo and iodo histidine", as opposed to the use of unsubstituted histidine or polyhistidine as required by claims 25 and 42 of the present application.

Inasmuch as neither Peterson et al. nor Reeck et al. nor Kothari et al., nor Burton et al. identically disclose or describe all of the claim recitations of the pending claims, as currently amended, the §102 rejections based on those four (4) references are untenable and should, therefore, be withdrawn.

B. The Combined Disclosures of Peterson et al., Reeck et al., Kothari et al., Burton et al. and the Sigma Catalog Fail to Render Obvious the Subject Matter of Claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66

All claim recitations must be considered in determining non-obviousness under 35 U.S.C. §103. In re Saether, 181 U.S.P.Q. 36 (C.C.P.A. 1974). It has long been held that when the Examiner disregards specific claim recitations that distinguish over the prior art, the rejection is improper and will be overturned. In re Glass, 176 U.S.P.Q. 489 (C.C.P.A. 1973). In the present case, the combined disclosures of Peterson et al., Reeck et al., Kothari et al., Burton et al. and the Sigma catalog clearly fail to provide evidence of obviousness with respect to charge switch materials having a pKa in the range of about 4.5 to about 8.5, as called for in applicant's claims. None of the cited references provide disclosure regarding this aspect of applicant's claims.

There is no dispute that Bis-Tris is itself a known biological buffer, but the prior art used to show its form solid phases having charge switch properties for purifying nucleic acid. As in the case of the §102 rejections discussed above, the Examiner's argument here is fatally flawed as it relies on references disclosing ECTHAM cellulose, which, as the Declarations of Matthew Baker and Garry Harper show, does not have a pKa suitable for use as a charge switch material, and which has properties more akin to prior art ion exchangers.

Furthermore, Peterson et al., Reeck et al. and Kothari et al. provide no information regarding the pKa of the ECTHAM

cellulose product described therein. As noted above, Burton et al. provide pKa information, but only with respect to ligands based on phenol or substituted phenol. It has long been recognized that silence in a reference is not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow. In re Burt, 148 U.S.P.Q. 548 (C.C.P.A. 1966).

For the above-stated reasons, the disclosures of Peterson et al., Reeck et al., Kothari et al., Burton et al. and the Sigma catalog, even if properly combinable in the matter proposed by the Examiner (which applicant disputes) do not provide response for all of the recitations of applicant's claims as now amended. That being the case, the 35 U.S.C. §103(a) rejection of claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66 based on that combination of references cannot be maintained.

- C. The Combined Disclosures of Peterson et al., Reeck et al., Kothari et al., the Sigma Catalog, Arnold, Jr. et al., Hornes et al. and Sommerton et al. Fail to Render Obvious the Subject Matter of Claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66

The additional references cited by the Examiner are relied on for their disclosures of completely general concepts, such as ionizable groups being polymerized or the solid phase being magnetic beads. None of these secondary references overcomes the fundamental defect in the Examiner's position, as noted above, which is that the pKa of ECTHAM cellulose makes it completely unsuitable for use as a charge switch material for purifying nucleic acid. Indeed, all three (3) secondary

references are concerned with methods of purifying nucleic acid that rely on the hybridization of a target nucleic acid molecule to a complimentary probe on the solid phase. As such, these references clearly fail to suggest to those of ordinary skill in the art the charge switch material of claims 25-27, 34, 42-44, 48, 51, 52, 56 and 66. Accordingly, the rejection of those claims based on this combination of references is improper and should be withdrawn.

D. The Combined Disclosures of Peterson et al., Reeck et al., Kothari et al., the Sigma Catalog, Arnold, Jr., et al., Hornes et al., Sommerton et al., Tooley and Grubs Fail to Render Obvious the Subject Matter of Claims 25-34, 42-68

The basic deficiencies in the disclosures of Peterson et al., Reeck et al., Kothari et al., the Sigma Catalog, Arnold, Jr., et al., Hornes et al., and Sommerton et al. have been set out in detail above. The Examiner's additional reliance on Tooley and Cobbs clearly fails to compensate for those deficiencies.

The proposed combination of references cited in support of this rejection would scarcely have been made by the person of ordinary skill in the art without some motivation provided in the references themselves which is plainly lacking.

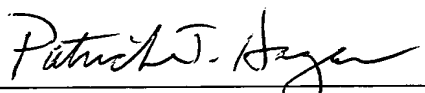
Applicant's position as to the general lack of relevance of Tooley and Cobbs to the present invention is set forth in the response to the June 18, 2002 Official Action and is incorporated by reference herein, so as not to unduly lengthen these remarks.

Suffice it to say, the §103(a) rejection of claims 25-34 and 42-68 based on the combined disclosures of Peterson et al., Reeck et al., Kothari et al., the Sigma Catalog, Arnold, Jr., et al., Hornes et al., Sommerton et al., Tooley and Grubbs cannot properly be maintained in view of the present amendment and should, therefore, be withdrawn.

In view of the present amendment, the Declarations of Matthew Baker and Garry Harper submitted herewith and the foregoing remarks, it is respectfully requested that the objections and rejections set forth in the April 9, 2003 Official Action be withdrawn and that this application be passed to issue and such action is earnestly solicited.

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Enclosures: Declaration of Matthew Baker  
Declaration of Garry Harper